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10/082,618	02/22/2002	Alan D. Olstein	7005-0003	4458
23980	7590	01/28/2004	EXAMINER	
REED & EBERLE LLP 800 MENLO AVENUE, SUITE 210 MENLO PARK, CA 94025			LUCAS, ZACHARIAH	
		ART UNIT	PAPER NUMBER	
		1648		
DATE MAILED: 01/28/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Applicant No.	Applicant(s)
	10/082,618	OLSTEIN ET AL.
	Examiner	Art Unit
	Zachariah Lucas	1648

-- The MAILING DATE of this communication appears on the cover sheet with the corresponding address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 30 October 2003.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-72 is/are pending in the application.
- 4a) Of the above claim(s) 5,10-63, and 68-72 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-4,6-9 and 64-67 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. §§ 119 and 120

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) All b) Some \* c) None of:  
1. Certified copies of the priority documents have been received.  
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) The translation of the foreign language provisional application has been received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) <input type="checkbox"/> Other: _____ .

## **DETAILED ACTION**

### *Status of the claims*

1. Currently claims 1-72 are pending, with claims 5, 10-63, 65, and 68-72 withdrawn as to non-elected subject matter, and with claims 1-4, 6-9, and 64-67 under examination. In the prior action, mailed on July 28, 2004, claims 1-4, 7-9, 64, 66, and 67 were rejected. Applicant's notation regarding the exclusion of claims 6 and 65 in the prior action is noted. In the Response filed on October 30, 2003, the Applicant amended claim 1.

2. It is noted that the further election of subgroups D and 1, upon the election of Group I, were not species elections as indicated by Applicant. However, the election of the metal cobalt (Co) was a species election. This is clear from the separation between elections among distinct inventions and species in the Restriction requirement. Nonetheless, as indicated in the requirement, linking claim practice does apply so long as there is an allowable linking claim (claim 1) among the separate inventions.

3. Because this Office action raises new grounds of rejection not necessitated by amendment, this action is made Non-Final.

### *Specification*

4. **(Prior Objection- Withdrawn)** The disclosure was objected to because of the following informalities: on page 42, lines 25-26, the discussion of Example 3 referred to "the Nisin-Co (II)

complex (of Example 3)." In view of the amendment to the specification, the objection is withdrawn.

***Sequence Listing***

5. **(New objection)** This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The paper sequence listing and CRF provided by the Applicant are not consistent with the sequences disclosed in the application. In particular, the residue 27 of SEQ ID NO: 5, which is disclosed as an isoleucine on Table I (page 17) of the specification, has been substituted with a threonine in the paper sequence listing and the CRF.

Applicant is given three months from the mailing date of this action within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

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6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. (**Prior Rejection- Maintained**) Claims 1-4, and 7 were rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The rejection is maintained, and extended to claims 6, 8, 9, and 64-68 for the reasons discussed below. Thus, claim 1-4, 6-9, and 64-68 are presently rejected under 35 U.S.C. 101 for reading on non-statutory subject matter. These claims read on chelated complexes of bacteriocins and a metal. The claims read on any such complexes, including both isolated complexes and complexes in the natural environment. The Applicant amended the claims to read on complexes formed in situ in a sample to be tested. However, there does not appear to be a limit on what comprises a sample to be tested. Such samples would include any animal tissues. See e.g., page 37. Pommer teaches that bacteriocins are secreted by bacteria within (e.g.) the intestinal tracts of animals. J Biol Chem 274(38): 27153, at 27158, right column. Thus, it is apparent that such compounds are produced by these bacteria. Therefore, it is also apparent the compounds are formed in situ in tissues that may be used as samples. The amendment does not therefore avoid the rejection.

The Applicant also contends that because the Pommer reference indicates that the metal is not essential to the bacteriocin's activity, whereas the metal is required for the presently claimed composition, the reference is not a demonstration that the claimed invention is a naturally occurring composition. The Applicant's attention is drawn to section 2113 of the MPEP, which states that the patentability of claimed products is determined by the product itself, and not by the process of making it unless such process affects the structure of the claimed

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product. The exceptional circumstance has not been shown in the present case. Thus, regardless of the teachings of Pommer regarding the requirements of the metal in the bacteriocin complexes, the reference teaches that the metals or nevertheless present in the protein's naturally occurring form. Because the additional claim language does not distinguish the claimed product from the naturally occurring product, the rejection is maintained.

Further, additional teachings in the art demonstrate that nisin and other lantibiotics have metal binding capabilities. See, Friedman, J Agricult Food Chem 47(4): 1295-319, abstract, and page 1312 (indicating that, due to structural peculiarities, the several lantibiotics, including nisin, are likely to have strong affinity for metals, including cobalt); and Surovoy et al., Peptides 1992, Proceedings of the European Peptide Symposium 22<sup>nd</sup>(1993), pages 563-64 (teaching the purification of a complex of prenisin and zinc at page 564). Thus, because the art teaches that nisin, and other lantibiotics have affinity for the identified metals, it is apparent that the complexes described by claims 6, 8, 9, and 64-68 also read on naturally occurring complexes. Thus, the rejection is extended to these claims, and maintained.

However, while the rejection is maintained for the reasons indicated above, it is noted that the prior action indicated that insertion of the term "isolated" to describe the complex in the claim will not satisfy this rejection because of the knowledge, and prior isolation. This statement is withdrawn as it does not appear that the isolated compound is itself found in nature. While this statement may be true with reference to an anticipation rejection, such is not the case for rejections under 35 U.S.C. 101. The Office apologizes for any inconvenience caused by the inclusion of this statement in the 101 rejection.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. (**New Rejection**) Claim 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on the claimed complexes wherein the bacteriocin is a peptide encoded by SEQ ID NO: 8, or a nucleic acid that hybridizes to that sequence under stringent conditions. However, there is no definition in the specification as to what hybridization conditions the Applicant considers to be "stringent." The claim thus includes relative terminology without a basis by which those in the art could determine what conditions the Applicant considers to be stringent. Thus, those in the art have not been apprised of the scope of the claim because they have been provided adequate information by which to determine what polynucleotides, and therefore what peptides, fall within the scope of the claim.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. (**New Rejection**) Claim 65 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes of a bacteriocin of SEQ ID NO: 8 and a metal, is not enabling for complexes comprising bacteriocins that hybridize under stringent conditions to SEQ ID NO: 8. This claim reads on a complex of a bacteriocin and cobalt, wherein the

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bacteriocin is "encoded by the nucleic acid of SEQ ID NO: 8 or a nucleic acid sequence that hybridizes with SEQ ID NO: 8 under stringent conditions." This is because coding sequence that hybridize to SEQ ID NO: 8 will not encode for bacteriocins, but will be the complementary strands to cDNAs that may encode a bacteriocin. The complementary strand however, if expressed would not produce a bacteriocin.

12. **(Prior Rejection- Maintained)** Claims 1-4, 6- 9, and 64- 67 were rejected in the prior action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on complexes of bacteriocins, or fragments, homologs, and variants thereof (collectively-variants), with a transitional metal. The Applicant traverses the rejection on the grounds that they have provided definitions of the terms in the specification, and that the terms do not merely define a goal, but a "well-known and commonly understood genus." However, the Applicant has not provided any evidence that this genus is so well known and understood. Further, the present case does not merely relate to variants of bacteriocins with antibiotic activity, but to those that maintain their ability to bind bacteria and to metal ions.

There do not appear to be any teachings in the art regarding the modification of bacteriocins in general, or lantibiotic or nisin in particular, such that both of these properties are maintained. Nor, as was pointed out in the prior action, has the Applicant provided any teachings regarding structural characteristics by which those in the art could identify such homologs or

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variants of the antibacterial peptides. Further, it is known that the art of peptide and protein modification is complex, and that the effects of modifying a particular residue in a sequence are, without specific teachings regarding the structure, and its relation to the function, of the protein, unpredictable. See e.g., Bowie et al., Science 247: 1306-10 (cited in the prior action, teaching that although proteins tend to be tolerant to amino substitutions, the effect of any particular substitution is unpredictable given that some residues are more or less important to the protein's structure and function). Because the Applicant has not provided any examples of variants that would meet the functional requirements of the claimed invention, and has not provided any information such that those in the art would recognize such variants, and be able to distinguish them from variants that would not bind both bacteria and metal ions, the Applicant has not provided adequate written description for the full scope of the claimed invention.

13. **(Prior Rejection- Maintained)** Claims 1-4, 6-9, and 64-67 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for complexes comprising a bacteriocin and a transition metal, does not reasonably provide enablement for complexes comprising bacteriocin variants and transition metals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. As indicated in the prior action, the claims read on complexes comprising a transition metal and a bacteriocin, or “fragments, homologs and variants thereof” (referred to collectively as “variants”). The Applicant traverses the rejection on the grounds that, in their view, consideration of the Wands factors favors a finding of enablement in the present application.

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As noted by the Applicant, enablement of claims is based on a consideration of the relevant factors as set forth in In re Wands, 8 U.S.P.Q.2d 1400 (Fed Cir 1988). It is further noted, that while consideration of all factors is required, only the relevant factors need be addressed. See e.g., MPEP 2164.04. In the present case, as the Applicant noted, the Examiner did not address each of the factors. However, the lack of discussion of these factors is not an implicit admission that the factors favor enablement, merely that the Examiner did not consider these factors as important in the final analysis as those actually discussed.

For example, the Applicant indicated that they consider the Examiner's silence regarding the quantity of experimentation as an indication that this factor favors enablement. This is an erroneous assumption. While the Examiner did not specifically discuss this factor, the factor does not favor a finding of enablement. In the Examiner's view this factor is, at best, a neutral factor. This is because, while the experiments that need be conducted to determine if a particular embodiment is operable may be considered routine, those in the art would be required to perform repeated rounds of experimentation as different set of variants are developed to determine whether or not such variants would be effective in the uses indicated by the Applicant. The Examiner found the factors of the nature of the invention, the relative skill of those in the art to be equally neutral.

However, contrary to the Applicant's assertion that the Examiner made no comments regarding the state of the art, it is noted that the Examiner cited the Bowie reference, which deals with the modification of proteins. While this reference was primarily used to demonstrate the unpredictability of the art, the Examiner considers such unpredictability to be a part of the state of the prior art in the present case. Further, while the art has frequent citations to the antibiotic

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effects of nisin, the search conducted by the Examiner found no references relating to the modification of this peptide, or lantibiotics or bacteriocins in general such that the functional activities and metal binding properties of the peptides was maintained. Thus, although the Examiner did not explicitly refer to this factor in the prior action, the Examiner does not consider the factor to favor a finding of enablement. Rather, the factor was simply less important to the determination than were the other factors that were discussed.

The Applicant also disagrees with the Examiner's conclusion regarding the guidance provided in the specification, the predictability of the art, and for the breadth of the claims. The Applicant's arguments in traversal of the Examiner's conclusions regarding these factors re not found persuasive.

The Applicant first argues that they have provided examples and guidance in the making of the variants. They point out for example that their specification identifies homologs of nisin as including peptides whose nucleic acids hybridize under stringent conditions to the sequence of SEQ ID NO: 8. The Applicant continues by arguing that other acceptable variants include "fusion proteins of any of the generally cationic peptides synthesized by bacteria, plants, mammals or insects having antimicrobial activity and forming complexes with transition or lanthanide metals..." However, while the Applicant has provided a list of some specific bacteriocines, the Applicant has not indicated what regions of those peptides are required for the functions indicated by this statement. One of ordinary skill in the art, looking at the structures of the disclosed peptide would not know from them what residues are required for their antimicrobial activity, or for the metal binding activity, and what modifications may be made to the peptides such that these functions are preserved. Thus, while the Applicant has provided

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examples and guidance as to unmodified bacteriocins, other than suggesting the hybridization techniques, they have provided no guidance as to what modifications may be made to bacteriocins such that the functional activities of the proteins that are essential to their operation are preserved.

The Applicant also argues that they are enabled for the use of variants and homologs of bacteriocins based on the teachings of the Gasson et al. reference cited in the prior office action, and used to support a rejection for the obviousness of the claimed complexes. However, while Gasson does indicate that the Applicant may be enabled for certain variants or homologs of nisin, the reference does not teach demonstrate that the Applicant is enabled for any homolog or variant of any bacteriocin or lantibiotic. This is because neither the art, nor the present application provides any teachings such that those in the art would be able to make and use, without undue experimentation, any variant of the peptides wherein the variants maintain both the necessary properties of binding bacteria and binding transition metal ions. The Applicant has provided no guidance, either by examples or by providing information as to how to modify the proteins such that these functions are maintained, for the manipulation of the proteins such that they would be operative in the claimed invention. Thus, the Examiner finds that neither of the factors of guidance or the presence of working examples favors the enablement of the claims to the extent that they read on complexes including variants of the peptides.

Finally, the Applicant argues that the Bowie reference does not provide indications as to the unpredictability of the art. The Applicant argues that the teachings of Bowie refer to difficulties encountered in the synthesis of new proteins, whereas the present claims are directed to modification of existing structures. This traversal is not found persuasive because, while the

body of the Bowie reference may be concerned with the synthesis of new proteins, the reference considers the problems encountered with reference to difficulties found in the art of protein structure versus functions studies as whole. For example, on page 1306, the authors of the article describe the problems of substitution tolerance with respect to the modification of an existing protein structure. Thus, while the authors of the reference may be concerned with the synthesis of new proteins, the teachings therein apply equally to the modification of existing structures.

The Applicant's arguments in traversal are not found persuasive for the reasons indicated above. The rejection is therefore maintained.

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. (**Prior Rejection- Maintained**) Claims 1-4, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Pommer et al., J Biol Chem, supra. The claims read on chelated complexes comprising a bacteriocin, and a transitional metal, including embodiments wherein the metal is Cobalt. Pommer discloses a bacteriocin that binds to the metals Zinc, Nickel, or Cobalt. Abstract. The reference further discloses that these complexes bind to and enter bacterium, including E. coli. Thus, the reference anticipates the identified claims.

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The Applicant traverses the rejection on the grounds that the amended claim 1, which indicates that the complex of the bacteriocin and the Co is formed in situ, distinguishes over the prior art. The Applicant argues that, because Pommer does not teach the purpose of the metal in the complex, those in the art would have had no motivation to form the complex in situ. The traversal is not found persuasive.

The Applicant is attempting to distinguish the claimed composition from that in the prior art based solely on the method of making the composition. However, the structures disclosed by Pommer meet all of the structural limitations of the claimed compositions. It is established law that the patentability of a product, even a product claimed as product-by-process, is determined by the structural limitations of the claimed product. See, MPEP § 2113. Because the Applicant has provided no reason to suspect that forming the complex in situ would alter the structure of the complex such that it differs from that in the art, the rejection is maintained.

16. **(New Rejection)** Claims 1-4, 6, 8, 64-67 rejected under 35 U.S.C. 102(b) as being anticipated by Surovoy et al. (supra). These claims have been described above. Surovoy teaches that the prenisin protein complexes with a transition metal. The reference also teaches that the metal is co-purified along with the synthetic protein, indicating that the authors had purified complexes of the metal and the protein. While the reference does not provide the specific sequence of the prenisin protein, they refer to by the same name as the protein of SEQ ID NO: 5, and indicate that the protein has 57 residues, including 5 cysteines, as does the peptide of SEQ ID NO: 5. The reference therefore appears to be describing a complex comprising the peptide of SEQ ID NO: 5 complexed with a transition metal, and therefore anticipates the identified claims.

***Claim Rejections - 35 USC § 103***

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. (**Prior Rejection- Reformed and Maintained**) Claims 1-4, 7, 8, 9, and 64 were rejected under 35 U.S.C. 103(a) as being unpatentable over Siddigi et al. (U.S. Patent 5,541,113), in view of Olstein et al., (U.S. Patent 5,750,357), and Timmer et al., EO 0659068. The rejection is reformed as follows: Claims 1-4, 6-9, and 64 are rejected over the teachings of Siddigi in view of Olstein, Meyer et al. (Arch Microbiol 167:67-77), and Friedman (J Agricult Food Chem 47(4): 1295-319). As indicated in the prior action, the claims read chelated complexes of bacteriocins, including lantibiotics, and the lantibiotic nisin, wherein the bacteriocin is complexed to a transitional metal, including cobalt. The Applicant traverses the rejection by arguing that the references cited in the prior action do not teach or suggest the claimed compositions. The Examiner agrees, in part, with the Applicant's basis for the traversal. This is because none of the previously cited references appears to indicate that nisin is capable of binding to a metal ion as would be required by one of ordinary skill in the art attempting to use nisin as the metal binding protein in the method of Siddigi.

The teachings of Siddigi, Olstein, and Meyer were described in the prior action. The Applicant's arguments regarding the deficiencies of the individual references are noted. However, these arguments are not found persuasive. The Applicant indicates that there would be

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no motivation for the combination of the Siddigi and Olstein references. The Examiner agrees that, without more, those in the art intending to apply the teachings of Siddigi would not necessarily look to the teachings of Olstein, because that reference does not teach the use of transition metals as labels. However, these two references are not the only reference cited in the rejection. Where claims are rejected as obvious over a combination of references, each of the references "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." In re Merck & Co., 231 USPQ 375, 380 (Fed. Cir. 1986). Thus, while the Siddigi and Olstein references do not alone teach or suggest the claimed invention, this does not demonstrate that the combined teachings of these references and others would not render the claims obvious.

The Applicant further argues that the Timmer reference, relied on by the Examiner to demonstrate that it would be obvious to one of ordinary skill in the art to look to nisin and the lantibiotics for use in methods of detection, would not have been looked to by those in the art considering the methods of Siddigi and Olstein. The Examiner does not agree. However, the reference is not included in the reformed rejection, which relies on the teachings of Meyer and Friedman to suggest the use of nisin and the lantibiotics.

As indicated in the prior action, Siddigi teaches the use of protein/metal complexes for the detection of analytes, particularly to transition metal of Group 8 of the periodic table (which include cobalt, iron, and nickel). Col 12., 50-59. Olstein teaches the use of chemically labeled biocides that bind bacteria for the detection of such microorganisms. Col 4, lines 15-24. One skilled in the art would be expected to be aware of each of these references as they are both concerned with the art of detecting analytes in a test sample.

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The Meyer reference indicates that nisin is a peptide with antimicrobial activity that binds to the cell membranes of target bacterium. Page 74, right column, first full paragraph. Freidman indicates that these proteins have a high affinity for metals such as cobalt, iron, zinc, and copper. Thus, from these references, it would have been obvious to use a cobalt/nsisin complex for the detection of bacteria. This is because the teachings of Siddigi and Olstein suggest, respectively, the use of a transition metal as a label for detecting analytes, and the use of a biocidal protein as a binding moiety for the detection of bacteria, and the teachings regarding nisin indicate that it would be a useful compound in detection methods according to the teachings of both the Siddigi and Olstein references. Because the art suggests a method of detecting bacteria using a method involving nisin and cobalt, the art renders obvious the claimed complex comprising nisin and cobalt. In view of the above, while the Examiner agrees that none of the teachings of the cited references, taken individually, would render obvious the claimed composition. However, as indicated above, the teachings of the references cumulatively do teach the limitations of the claimed complex.

19. **(Prior Rejection-Reformed and Maintained)** Claims 66 and 67 were rejected under 35 U.S.C. 103(a) as being unpatentable over Siddigi, Olstein, and Timmer as applied to claims 1-4, 7, 8, 9, and 64 in that action, and further in view of Gasson et al., WO 96/16180. For the reasons indicated above, this rejection is restated as follows: Claims 66 and 67 are rejected as obvious under 35 U.S.C. 103(a) over the teachings of Siddigi in view of Olstein, Meyer, and Friedman, and further in view of Gasson. These claims describe the method indicated above, wherein the bacteriocin has an amino acid sequence having either, respectively, a substitution, addition, or

deletion of 1-3 residues from, or that is 90% homologous with, the sequence of SEQ ID NO: 5 of the application (disclosed as nisin precursor on page 17 of the application).

The Applicant traversed the rejection of claim 66 and 67 for the same reasons as indicated with respect to claims 1-4, 7-9, and 64. This traversal is considered overcome by the reformed rejection.

**20. (New Rejection)** Claims 1-5, 6-9, and 64-67 are rejected as obvious over the teachings of Siddigi in view of Olstein, Meyer, and Friedman as applied above, further in view of Buchman et al. (J Biol Chem 263(31): 16260-66). The claims have been described in part above. Claims 65 further requires that the nisin be encoded by a polynucleotide of SEQ ID NO: 8 under stringent conditions. Claims 66 and 67 require that the nisin comprises the amino acid sequence of SEQ ID NO: 5. For the purposes of this action, SEQ ID NO: 5 is considered to be the sequence provided in Table I of the application, and not the sequence provided in the paper and CRF copies of the sequence listing. The teachings of Siddigi, Olstein, Meyer, and Friedman have been described above. Buchman teaches that nisin is encoded by the nucleotide sequence of Accession J04057 (sharing 100% identity with SEQ ID NO: 8), and has the amino acid sequence of Accession AAA88606 (sharing 100% identity with the sequence disclosed in Table I as SEQ ID NO: 5). Because the references indicated above render obvious a complex of nisin and cobalt, it would have been obvious to those in the art to use the nisin described by the Buchman reference.

### *Conclusion*

21. No claims are allowed.

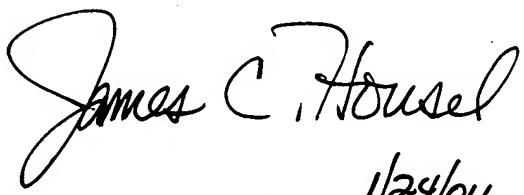
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22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
Z. Lucas  
Patent Examiner  
January 21, 2004

  
James C. Housel  
1/24/04  
JAMES HOUSEL  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600